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EXAMINER
KUBELIK, ANNE R

ART UNIT	PAPER NUMBER
1638	

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14

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,243	KAPULNIK ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *3,5,8,15-17,23,30,34 and 39-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6,7,9-14,18-22,24-29,31-33,35-38 and 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *with the appplication* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election of Group I (claims 1-2, 4, 6-7, 9-14, 18-22, 24-29, 31-33, 35-38 and 50-53 to the extent they read on a method of degenerating plant tissue by expressing a protein that binds biotin) in Paper No. 13 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). The restriction is made FINAL. Claims 3, 5, 8, 15-17, 23, 30, 34 and 39-49 are withdrawn from consideration as being drawn to non-elected inventions.

2. The disclosure is objected to because poor copy quality could result in printing errors. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a).

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed; and (3) a request for its entry.

3. The drawings are objected to for the reasons indicated on the accompanying form PTO 948. Corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. See 37 CFR 1.85(a) and MPEP 608.02(b).

Claim Objections

4. Claims 1, 7, 13-14, 18, 22, 24, 26, 28, 33, 38 and 53 are objected to because of the following informalities:

The comma after "fashion" in claim 1, line 5, and claim 18, line 3, should be deleted.

In claims 7, 22 and 33 the "and" at the end of the 2nd line should be replaced with a comma.

The following claims have an improper article before a word: Claim 13 before "morphology" in line 2, claim 14 before "development" in line 2, claim 24 before "cytoplasm" in line 2, claim 26 before "cytoplasm" in line 3, and claim 38 before "cytoplasm" in line 2.

In claim 28, line 6, --wherein-- should be inserted before "said" in line 3 and "encoding" should be replaced with --encodes-- in line 4.

In claim 53, line 6, --wherein-- should be inserted before "said" and "being" should be replaced with --are--.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, 4, 6-7, 9-14, 18-22, 24-29, 31-33, 35-38 and 50-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for streptavidin-encoding constructs with a plant signal sequence for secretion (the αβ gliadin storage protein signal sequence) and the streptavidin processing sequences, and with and without the bacterial

streptavidin signal peptide, expressed from a constitutive promoter, methods of using them to tarfsorm plants, and plants so obtained, does not reasonably provide enablement for constructs encoding any biotin-binding protein, including derivatives of biotin and streptavidin, proteins without a secretion signal sequence or streptavidin with the processing sequences, methods of using them to transform plants, plants so obtained, or methods of plastid transformation with a construct encoding a biotin-binding protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to methods of effecting degeneration of somatic plant tissue by transformation of a plant with a construct encoding any biotin-binding protein, including derivatives of biotin and streptavidin or without a secretion signal sequence, or methods of plastid transformation with a construct encoding a biotin-binding protein.

The instant specification, however, only provides guidance for construction of streptavidin-encoding constructs with and without a plant signal sequence for secretion (the αβ gliadin storage protein signal sequence), the bacterial streptavidin signal peptide, and the streptavidin processing sequences, expressed from the CaMV 35 S promoter (Figure 2; pg 43-44), their transformation into tomato (pg 44) and testing for the presence of the streptavidin gene in transformants by PCR, and Southern and Northern blotting (pg 44-46). Only the constructs that comprised a plant signal sequence for secretion and the streptavidin processing sequences did not cause severe necrosis (pg 46-47), and plants transformed with a construct comprising a plant signal sequence for secretion, the bacterial streptavidin signal peptide, and the streptavidin processing sequences were analyzed further - most died before maturity and/or displayed

abnormal morphology, but spraying biotin on the plants stopped degeneration (pg 47-48 and 50). Seeds from the plants had reduced germination that could be restored by application of biotin (pg 49). Plants transformed with a construct encoding streptavidin expressed from the root specific Tob promoter were female sterile and had fruit tissue degeneration (pg 48).

The instant specification fails to provide guidance for methods of plastid transformation with a construct encoding a biotin-binding protein or for methods of effecting degeneration of somatic plant tissue by transformation of a plant with a construct encoding any biotin-binding protein, including derivatives of biotin and streptavidin or with constructs that do not have a secretion signal sequence.

The instant specification fails to provide guidance for methods of isolation or construction of derivatives or "modificants" of biotin or streptavidin or "modificants" or derivatives of biotin or streptavidin.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate nucleic acids encoding biotin-binding proteins that are derivatives or "modificants" of avidin or streptavidin or modificants of the derivatives. Making all possible single amino acid substitutions in a 128 amino acid long protein like avidin would require making and analyzing 19^{128} nucleic acids, and making all possible single amino acid substitutions in a 184 amino acid long protein like streptavidin would require making and analyzing 19^{184} nucleic acids.

As the specification does not describe the transformation of any plant with a gene encoding derivatives of avidin or streptavidin, undue trial and error experimentation would be required to screen through the myriad of nucleic acids encompassed by the claims and plants

transformed therewith, to identify those with degeneration of somatic plant tissue, if such plants are even obtainable.

The examples in the specification teach that a plant signal sequence for secretion is an essential feature of the constructs; all seedlings transformed with a construct without this sequence died (see, *e.g.*, pg 46, lines 19-29, and table 3). This essential feature is missing from the constructs of the broadest claims.

Given the claim breath, unpredictability in the art, undue experimentation, and lack of guidance in the specification as discussed above, the instant invention is not enabled throughout the full scope of the claims.

7. Claims 1-2, 4, 6-7, 9-14, 18-22, 24-29, 31-33, 35-38 and 50-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a multitude of DNA constructs encoding any biotin-binding protein, including derivatives of biotin and streptavidin, and methods of their use.

In contrast, the specification only describes streptavidin-encoding constructs operably linked to the αβ gliadin storage protein signal sequence and the streptavidin processing sequences, and with and without the bacterial streptavidin signal peptide. Applicant does not describe other DNA molecules encompassed by the claims, and the structural features that distinguish all such nucleic acids from other nucleic acids are not provided.

Hence, Applicant has not, in fact, described DNA molecules that encode a biotin-binding protein within the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and physical characteristics of the claimed compositions, it is not clear that Applicant was in possession of the genus claimed at the time this application was filed.

See *Univ. of California v. Eli Lilly*, 119 F.3d 1559, 43 USPQ 2d 1398 (Fed. Cir. 1997):

> The name cDNA is not in itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA .... Accordingly, the specification does not provide a written description of the invention ....

and at pg 1406:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicted, does not suffice to define the genus because it is only an indication of what the genes does, not what it is.

See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ 2d 1016 at page 1021:

> A gene is a chemical compound, albeit a complex one, and ... conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials .... Conception does not occur unless one has a mental picture of the structure of the chemical or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by it principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-2, 4, 6-7, 9-14, 18-22, 24-29, 31-33, 35-38 and 50-53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections.

Claims 1 and 18 are indefinite in their recitation of "fashion". Does this term mean method, custom, in the current mode or something else entirely, and how do these uses apply to expression of a protein?

Parts (i) to (v) of claims 2 and 19 do not make sense as criteria for selection of the "fashion" of expression of a heterologous protein in a plant. For example, it is not clear how the level of expression of a heterologous protein can be used to determine the "fashion" in which the protein is expressed. It is not clear, for example, what the level of expression - is this the desired level in the transformed plant? The level of the expression of the protein in its native source? Something else entirely?

Claim 7 is indefinite for being dependent upon claim 16. Claim 16 is drawn to a method, not a transgenic plant.

Claims 7, 22, 26 and 33 are indefinite in their recitation of " biotin binding derivatives" and "modificants thereof". First, it is not clear in what manner the derivatives differ from avidin and streptavidin. Second, "modificant" is not an English word, nor is it a word used by those of skill in the art. Presuming the word is intended to mean "variant", it is not clear in what manner the "modificants" differ from the derivatives, nor it is clear the extent or manner the "modificants" differ from avidin and streptavidin. Thus, the metes and bounds of the claimed invention are unclear.

Claim 28 is indefinite in its recitation of "A transgenic plant comprising somatic plant cells being transformed". Applicant appears to be claiming a plant only while its cells are in the process of being transformed. If this is not the case, it is suggested it is suggested that "being" be deleted.

Claim 31 is indefinite of its recitation of "where said promoter is a plant derived promoter s and plant virus derived promoter". A promoter cannot be from two unrelated sources. Additionally, "plant promoter" in parent claim 28 implies that the promoter is derived from a plant, and thus it cannot be derived from a virus.

Claim 53 is indefinite in its recitation of "said second, ... being in frame" in line 6. It is not clear what the segments are in frame relative to, nor is it clear what frame this is. Does it refer to an open reading frame?

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

11. Claims 1-2, 4, 6-7, 9, 13-14, 18-22, 24, 28-29, 31-33, 38 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Howard et al (WO 96/40949).

Howard et al teach nucleic acid expression cassette comprising a sequence encoding avidin (a biotin-binding protein) operably linked to an anther-specific promoter or the constitutive ubiquitin promoter, as well as a method of plant transformation therewith (pg 17-19, 24-31 and claims 1-13, 20-23 and 25). Expression of said sequence leads to male sterility because of degeneration of tissue and would result in control of morphology and development of the plant. Anther tissue is somatic because it is not germ-line tissue. Plant viability is maintained (see, *e.g.*, pg 26, paragraph 3). Expression of avidin would inherently be in the cytoplasm because that is where the ribosomes are located. Anther-specific promoters like the maize 5126 promoter, the maize SGB6 promoter, and the maize G9 promoter, are plant derived (pg 16-18). Avidin would inherently deplete bound and unbound biotin the tissue.

12. Claims 1-2, 4, 6-7, 9, 12-14, 18-22, 24, 27-29, 31-33, 37-38, 50 and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Baszczynski et al (1998, US Patent 5,767,379).

Baszczynski et al teach a nucleic acid expression cassette comprising a sequence encoding a signal sequence for secretion (the barley alpha amylase signal sequence) and a sequence encoding a biotin-binding protein (avidin), operably linked to the constitutive ubiquitin promoter, as well as method of plant transformation therewith (column 10, line 54, to column 11, line 36). Expression of said sequence leads to male sterility because of degeneration of tissue and would result in control morphology and development of the plant (column 7, lines 5-9). Anther tissue is somatic because it is not germ-line tissue. Plant viability is maintained (see, *e.g.*, column 11, lines 34-36). Expression of avidin would inherently be in the cytoplasm; the secretion signal sequence would first target the protein to the endoplasmic reticulum, as targeting

to the ER is essential for secretion. Avidin would inherently deplete bound and unbound biotin the tissue.

13. Claim1-2, 4, 6-7, 9, 12-14, 18-22, 24, 27-29, 31-33, 37-38, 50 and 52-53 rejected under 35 U.S.C. 102(e) as being anticipated by Albertson et al (US Patent 5,962,769, filed July, 1997).

Albertson et al teach transformation of plants with a nucleic acid comprising a sequence encoding a signal sequence for secretion (the barley alpha amylase signal sequence) and a sequence encoding a biotin-binding protein (avidin or streptavidin), expressed from an anther-specific promoter or the constitutive ubiquitin promoter (claims 1-42; column 7, lines 49-56; column, 18, line 49, to column 20, line 11). Such expression leads to male sterility because of degeneration of tissue and would result in control morphology and development of the plant. Anther tissue is somatic because it is not germ-line tissue. Plant viability is maintained (see, *e.g.*, column 20, lines 1-11). Expression of avidin would inherently be in the cytoplasm because that is where the ribosomes are located. Anther-specific promoters like the maize 5126 promoter, the maize SGB6 promoter, and the maize G9 promoter, are plant derived (column 12, line 14, to column 13, line 48). Avidin would inherently deplete bound and unbound biotin the tissue. The streptavidin sequence would inherently comprise a sequence encoding a bacterial signal peptide.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a), which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-2, 4, 6-7, 9-14, 18-22, 24-29, 31-33, 36-38 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baszczynski et al (1998, US Patent 5,767,379) in view of Mariani et al (1997, US Patent 5,689,041).

The claims are drawn to methods of effecting degeneration of somatic plant tissue by transformation of a plant with a construct encoding a biotin-binding protein operably linked to a plastid or mitochondrial targeting sequence.

The teachings of Baszczynski et al are discussed above. Baszczynski et al do not disclose a method of effecting degeneration of somatic plant tissue by transformation with a nucleic acid comprising a sequence encoding a signal sequence for plastid targeting operably linked to a sequence encoding a biotin-binding protein.

Mariani et al teach a method of effecting degeneration of somatic plant tissue by transformation with a nucleic acid comprising construct encoding a toxic protein (barstar) operably linked to a plastid or mitochondrial targeting sequence, such that the toxic protein is expressed in plastids or mitochondria (claims 3 and 30).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of effecting degeneration of somatic plant tissue taught by Baszczynski et al, to express avidin as a plastid-targeted protein as described in Mariani et al. One of ordinary skill in the art would have been motivated to do so because substitution of one toxic protein, avidin, for another toxic protein is an obvious design choice.

16. Claims 1-2, 4, 6-7, 9-10, 12-14, 18-22, 24-25, 27-29, 31-33, 35, 37-38, 50 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baszczynski et al (1998, US Patent 5,767,379) in view of Maliga (1996, US Patent 5,530,191).

The claims are drawn to methods of effecting degeneration of somatic plant tissue by transformation of a plant plastid with a construct encoding a biotin-binding protein.

The teachings of Baszczynski et al are discussed above. Baszczynski et al do not disclose a method of effecting degeneration of somatic plant tissue by plastid transformation with a nucleic acid comprising a sequence encoding a biotin-binding protein.

Maliga teaches a method of effecting degeneration of somatic plant tissue by plastid transformation with a nucleic acid comprising a sequence a toxic protein, including an RNAse, a protease, and a DNAse, such that the toxic protein is expressed in plastids (claims 1-18).

At the time the invention was made, it would have been obvious to one of ordinary skill in the art to modify the method of effecting degeneration of somatic plant tissue taught by Baszczynski et al, to express the protein in the plastid as described in Maliga. One of ordinary skill in the art would have been motivated to do so because substitution of one toxic protein, avidin, for another toxic protein is an obvious design choice.

Conclusion

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, whose telephone number is (703) 308-5059. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (703) 306-3218. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Anne R. Kubelik, Ph.D.
November 21, 2002

Amy Nel

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